REMARKS

Claims 1-19 are pending and stand rejected. Claims 1 and 17 have been amended to define the invention more clearly. Applicants have amended claims 1-2, 5-10, 12, 14 and 16-19. The amendments are made to clarify the subject matter claimed and place the claims in better form for examination. No new matter is added by the amendments, which are supported by the specification as originally filed. In view of the following discussion, the applicants submit that all pending claims are in condition for allowance.

In the Office Action at paragraph 5 claims 1-16 were rejected under 35 U.S.C. §103(a) as being obvious over Cornelissen, CAB8-Computer Applications in Biotechnology, June 25-27, 2001 ("Cornelissen") in view of Major, Biotechnology and Bioengineering, vol. 34, pp 592-599 (1989) ("Major"), and U.S. Published Application No. 2002/0138454 A1 to Gruenberg ("Gruenberg"), and further in view of United States Patent No. 6,402,941 to Lucido ("Lucido") and United States Patent No. 6,599,735 to Bartok ("Bartok"). Applicants traverse the rejection.

Amended claim 1 above recites, in part, certain salient features including the steps of measuring the cell concentration of the product in the bioreactor and in response to a signal from the analytical system the harvest pump moves concentrated retentate from said bioreactor to said second harvest receptacle; and wherein a second regulator receives a signal from a weighing device which measures the weight of the bioreactor, compares the weight of said bioreactor with a desired weight stored in a second reference operator, and, based on the comparison of the measured weight and the desired weight said second regulator sends a control signal to an upstream feed pump, which sends medium to the bioreactor from said upstream feed receptacle.

It is helpful to note that one of the stated objects of the present invention is to improve the fermentation and filtration process so as to make it possible to achieve the aim of the membranes of the cross-flow filtration unit having a service life which is as long as possible at the same time as the cell productivity is as high as possible. This object is achieved by it being possible to feed other substances, in addition to the medium, to the bioreactor in a controlled manner, by it being possible to harvest the concentrated retentate and the permeate in a controlled manner, and by the fermentation process and the filtration being regulated, in a manner in which they are matched to each other in an integrated system, by way of a control unit.

One skilled in the art viewing Cornelissen would be led away from looking to Major to achieve the subject matter of claim 1, and specifically, to add a second harvest receptacle for receiving directly retentate removed from the bioreactor. A reference teaches away from a modification when a person of ordinary skill, upon examining the reference, would be discouraged from making such modification. *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). Further, where the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, the proposed modification would not have been obvious. *See Tec Air Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999); *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

Cornelissen relates to a bioreactor system with a microfiltration unit linked as a bypass directly to the reactor. Cornelissen very clearly teaches the skilled artisan to continuously recycle cells and cell fragments through the filtration unit, and not to remove or separate materials from the bioreactor/filtration system, except as filtered product harvest. Removing any other material would upset the entire system of Cornelissen,

because the volume of the system in Cornelissen is handled by automated controls, including at least flow diffusion analysis (FDA) of methanol via a dialysis probe; control of methanol by a feed rate; and the measuring/monitoring of glycerol feed with an in-line filtration probe. The Examiner states the suggestion for employing a waste receiver as suggested by Major would have been to maintain a constant volume in the fermenter. As stated above, the skilled artisan viewing Cornelissen would not want to remove material to maintain a constant volume – the volume of material in Cornelissen is controlled by other means through sensors which control feed. As product is removed via filtration, feedstock is added. Hence, a skilled artisan reviewing Cornelissen would be discouraged from adding a waste receiver, and the removal of any volume from the reactor according to Major would render Cornelissen inoperative. The modification, therefore, would not have been obvious.

A further basis that the combination of Cornelissen and Major is improper is that the Examiner's stated support for the suggestion comes from the Major reference (p. 594, first paragraph, lines 7-9), not Cornelissen. Applicants submit in order for the combination to have been properly made the suggestion must have come from the primary reference. Withdrawal of the rejection on this ground is requested.

For the foregoing reasons the Applicants submit the Cornelissen and Major references cannot be combined. The Examiner does not rely on any of the remaining references for disclosure that remedies the above-discussed deficiencies. Since none of the remaining references disclose or suggest the method of claim 1 which requires withdrawal of retentate to a second harvest receptacle, the combination of the references cannot render amended claim 1 obvious. Claims 2-16 which depend from claim 1 and include further features are likewise not obvious, and are patentable.

Even assuming for argument's sake the Major reference could be combined with Cornelissen, which is not conceded, Applicants submit the examiner has failed to establish a prima facie case of obviousness based on the references cited. The combination of the references does not result in the subject matter of claim 1. Some deficiencies of Cornelissen and Major are discussed above. Further deficiencies are described below.

In paragraph 11 of the Office Action the Examiner compares the weighing device in Cornelissen to the system for measuring and readjusting nutrient medium in the bioreactor of the present invention. Applicants submit that the disclosure in Cornelissen does not teach the elements currently recited in claim 1. Specifically the weighing device in Cornelissen is connected to a pump on the downstream side of the bioreactor, wherein the downstream pump connects a product harvest receptacle and a microfiltration device, both of which are also on the downstream side of the bioreactor. This disclosure is not analogous at all to the recitation in claim 1 wherein a second regulator receives a signal from a weighing device which measures the weight of the bioreactor, compares the weight of said bioreactor with a desired weight stored in a second reference operator, and, based on the comparison of the measured weight and the desired weight said second regulator sends a control signal to an upstream feed pump, which sends medium to the bioreactor from said upstream feed receptacle.

At paragraph 8 of the Office Action, the Examiner has provided no reasonable basis for interpreting Gruenberg, which does not include any analyzer connected to the referenced pump, to disclose or even suggest that a control unit which is connected to a process computer would indicate changes within the bioreactor that would initiate the pump to withdraw product from the bioreactor. Gruenberg teaches the use of a

Mettler balance in combination with a peristaltic pump and a software solution which may be connected with the bioreactor or to nutrient medium containers. *See* Paragraphs 0060, 0109 and 0121. However, these elements do not disclose or suggest the control unit, analytical system, sensor for measuring cell concentration, analyzer, first regulator, and first reference operator as recited in claim 1. The Examiner has only generally described processes in Gruenberg and extrapolated their relevance to the specifically recited elements in the present claims. Further, since the elements disclosed in Gruenberg relate to a method for measuring nutrient feed or reactor weight, they have no relation to the specific measuring and removing of cell concentration recited in claim 1. *See* Gruenberg at paragraphs 0019, 0064, 0109, 0121-0122.

Moreover, Gruenberg never discloses that the device for measuring the weight of the bioreactor is directly connected to anything but a discharge pump (not a feed pump) and that while the nutrient feed receptacles are connected to a balance, software and pumps, they are not directly connected to a device for measuring the weight of the bioreactor and cannot be used to remove cell-contaminated medium from the bioreactor to a second harvest receptacle. Therefore the claim elements related to the first regulator and second regulator are not disclosed or suggested by Gruenberg.

The Lucido reference cannot cure the deficiencies of the foregoing references. Lucido discloses an apparatus for biological treatment of environmental contaminants and waste. The teachings highlighted by the Examiner in Lucido are contained in col. 8, lines 30-35, which teach that an optical sensor can be used to measure turbidity in the bioreactors, and that a higher turbidity can indicate a higher viable cell concentration. *See id.* Applicants submit that the above teaching does not render obvious the recited claim elements in claim 1, which include harvesting concentrated retentate and

permeate in a controlled manner and wherein said fermentation process and the filtration are regulated in an integrated system, by a control unit, wherein cell concentration is measured and regulated in said bioreactor by said control unit which further comprises an analytical system which measures the cell concentration using a sensor which is arranged in the bioreactor, wherein the sensor is connected to an analyzer which is connected to a first regulator which compares the actual value of cell concentrate with the desired value of a first reference operator.

The only disclosure in Lucido is to a process that recites an "alarm is hooked up to a computer via telephone lines which relays the sounding of the alarm to a central station. At this station the problem can be assessed and a repair unit dispatched as needed". *See* Lucido at col. 8, lines 36-40. Applicants submit there is no disclosure of how to combine the computer controlled system of Gruenberg with the turbidity sensor of Lucido with Cornelissen and Major to achieve the subject matter of claim 1, at least because in addition to the shortcomings recited above, neither Gruenberg or Lucido teach a procedure to automate the process based on the results of a turbidity sensor. Conjecture, speculation and the assumption of undisclosed elements plus a hypothetical combination of multiple unrelated references cannot be grounds for an obviousness rejection.

Furthermore, because Lucido is related to a process for removing industrial waste from sewage systems, Applicants submit that this is non-analogous art, and therefore would not be used by a person skilled in the art looking to add to the teachings of Major, Cornelissen and/or Gruenberg.

Bartok cannot cure the shortcomings of the cited references. The device in Bartok only contains a single harvest receptacle which is employed for receiving "fermentation broth". Bartok merely discloses a controller for operating an upstream pump.

Applicants submit that in view of the foregoing deficiencies the only way a person skilled in the art could combine Cornelissen, Major, Gruenberg, Lucido and Bartok and arrive at the subject matter of claim 1 would require the present specification as a template, along with modifications so that the deficiencies of the reference teachings could be adapted to the subject matter of claim 1. The instructions as to how to successfully practice the methods claimed can only be found in the present specification. Thus, it is clear the reason for combining all the references relied upon by the Examiner comes from the applicants' disclosure rather than coming from the applied prior art and that, therefore, the Examiner used impermissible hindsight in rejecting the claims. See, *W.L. Gore & Assoc. v. Garlock*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

Because the combined references do not teach or suggest each and every element of claims 1-16, it is requested that the above §103(a) rejection be withdrawn.

In paragraphs 23-28 of the Office Action the Examiner rejected claims 17-19 under 35 U.S.C. §103(a) as being obvious over Cornelissen in view of Major and Gruenberg and further in view of Bartok.

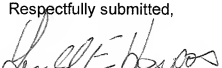
Applicants submit the rejection is overcome in view of the amendments and arguments herein. Amended claim 17 is recited above and shares certain features with claim 1, which have been shown to be absent in the prior art hereinabove. For the reasons for patentability stated above with respect to claim 1, *i.e.*, that one skilled in the art viewing Cornelissen would be led away from the Major reference, that such a combination would render Cornelissen inoperable and the combination of the references does not result

in the claimed subject matter, applicants submit claim 17 is likewise patentable. Dependent claims 18-19 all incorporate each and every limitation of claim 17, and therefore are also patentable.

Therefore, it is requested that the §103(a) rejection with regard to claims 17-19 be withdrawn.

In view of the foregoing, Applicants submit that the instant claims are in condition for allowance. Early and favorable action is earnestly solicited. The Examiner is urged to contact applicant's attorney at the number below to expedite the prosecution of this application.

Respectfully submitted,



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Date: July 1, 2010